

66-

This Page Is Inserted by IFW Operations  
and is not a part of the Official Record

## **BEST AVAILABLE IMAGES**

Defective images within this document are accurate representations of the original documents submitted by the applicant.

Defects in the images may include (but are not limited to):

- BLACK BORDERS
- TEXT CUT OFF AT TOP, BOTTOM OR SIDES
- FADED TEXT
- ILLEGIBLE TEXT
- SKEWED/SLANTED IMAGES
- COLORED PHOTOS
- BLACK OR VERY BLACK AND WHITE DARK PHOTOS
- GRAY SCALE DOCUMENTS

**IMAGES ARE BEST AVAILABLE COPY.**

**As rescanning documents *will not* correct images,  
please do not report the images to the  
Image Problem Mailbox.**



Europäisches Patentamt  
European Patent Office  
Office européen des brevets



(11) Publication number: 0 647 656 A1

(12)

# EUROPEAN PATENT APPLICATION

(21) Application number: 94305706.7

(51) Int. Cl.<sup>6</sup>: C07K 14/63, A61K 38/10

(22) Date of filing: 01.08.94

AE

(30) Priority: 06.08.93 US 103489

(43) Date of publication of application:  
12.04.95 Bulletin 95/15

(84) Designated Contracting States:  
BE CH DE FR GB IT LI NL SE

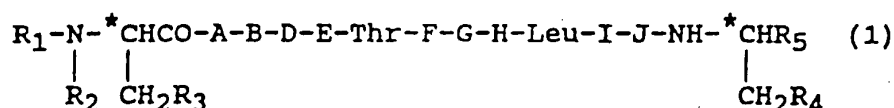
(71) Applicant: Ohmeda Pharmaceutical Products  
Division Inc.  
110 Allen Road  
Liberty Corner, New Jersey 07938-0804 (US)

(72) Inventor: Macielag, Mark J.  
8 Seneca Trail  
Branchburg, New Jersey 08876 (US)  
Inventor: Dharanipragada, Ramalinga  
25 Hickory Place, No G-5  
Chatham, New Jersey 07928 (US)  
Inventor: Marvin, Mary Sue  
86 Washington Street  
Morristown, New Jersey 07960 (US)

(74) Representative: Wickham, Michael et al  
c/o Patent and Trademark Department  
The BOC Group plc  
Chertsey Road  
Windlesham Surrey GU20 6HJ (GB)

(54) Motilin-like polypeptides that inhibit gastrointestinal motor activity.

(57) This invention pertains to polypeptides having gastrointestinal motor inhibitory activity represented by the formula:



including optically active isomeric forms and the pharmaceutically acceptable acid addition salts thereof wherein A is the L-stereoisomer of a lipophilic aliphatic or alicyclic amino acid; B is selected from the group consisting of L and D aromatic, heteroaromatic, lipophilic aliphatic, and alicyclic amino acids; D is the L-stereoisomer of a lipophilic aliphatic or alicyclic amino acid; E is the L-stereoisomer of an aromatic, aliphatic, or alicyclic amino acid; F is the L-stereoisomer of an aromatic or heteroaromatic amino acid; G is glycine or D-alanine; H is L-glutamic acid or L-glutamine; I is L-glutamine, L-glutamic acid, or L-alanine; J is a direct bond between I and group -NH- or is selected from the group consisting of Z, Z-Leu, Z-Leu-Gln, Z-Leu-Gln-Glu, Z-Leu-Gln-Glu-Lys, Z-Leu-Gln-Glu-Lys-Glu, Z-Leu-Gln-Glu-Lys-Glu-Arg, Z-Leu-Gln-Glu-Lys-Glu-Arg-Asn, Z-Leu-Gln-Glu-Lys-Glu-Arg-Asn-Lys, and Z-Leu-Gln-Glu-Lys-Glu-Arg-Asn-Lys-Gly, wherein Z is selected from the group consisting of arginine, D-arginine, D-homoarginine, D-lysine, D-ornithine, D-2,4-diaminobutyric acid, D-glutamine, D-asparagine, and D-alanine; R<sub>1</sub> and R<sub>2</sub> are independently hydrogen or lower-alkyl; R<sub>3</sub> is selected from the group consisting of lower-alkyl, cycloalkyl, substituted and unsubstituted aryl, and heteroaryl, wherein the aryl group may be substituted with one or more substituents selected from the group consisting of halogen, hydroxy, and lower-alkoxy; R<sub>4</sub> is selected from the group consisting of -CH<sub>2</sub>CONH<sub>2</sub>, aminoalkyl groups containing from 1 to 3 carbon atoms, and guanidinoalkyl groups containing 2 or 3 carbon atoms; R<sub>5</sub> is -COOH or -CONH<sub>2</sub>; and the symbol \* represents an asymmetric carbon atom which may be in the D or L configuration, and each lower-alkyl group contains from 1 to 4 carbon atoms, with the proviso that R<sub>4</sub> is -CH<sub>2</sub>CONH<sub>2</sub> only when J is Z-Leu or Z-Leu-Gln-Glu-Lys-Glu-Arg-Asn-Lys-Gly.

This invention relates to novel polypeptides having potent gastrointestinal motor inhibitory activity useful in the treatment of conditions characterized by elevated plasma motilin levels such as infectious diarrhea and Crohn's disease.

Motilin is a gastrointestinal linear polypeptide hormone which stimulates the gastric antrum, duodenum, and colon. Although its effects are not completely known, motilin plays a role in increasing gastric motility and stimulating pepsin output and may also be important in regulating the interdigestive myoelectric complex. Human motilin has not yet been purified, but its immunologic properties strongly suggest that it is very similar to porcine motilin. Porcine motilin contains 22 amino acid residues and may be represented by the formula:



Porcine motilin has a hydrophobic region from positions 1 to 5, a hydrophilic region from positions 11 to 22, and a connecting region from positions 6 to 10. Porcine motilin also has an  $\alpha$ -helical secondary structure from residues 9 to 20 of the primary sequence [Khan et al., *Biochemistry* 29, 5743-5751 (1990)].

Administration of motilin to healthy human subjects accelerates intestinal transit time and enhances gastric emptying. *In vitro*, motilin stimulates contractions of human and rabbit duodenal smooth muscle strips and isolated gastrointestinal smooth muscle cells. In addition, motilin and some of its derivatives compete with radiolabelled motilin for binding sites on human and rabbit antral tissue suggesting that stimulation of specific receptors in the gastrointestinal tract is responsible for the physiological effects of the hormone. Infusion of motilin has been reported to stimulate the emptying of solids and liquids in patients with diabetic gastroparesis [Peeters et al., *Gastroenterology* 100, A480 (1991)]. In addition, motilin has been used to treat patients with paralytic ileus caused by carcinoma of the gastrointestinal tract [Meyer et al., *Med. Klin.* 86, 515-517 (1991)]. Motilin has a relatively short half-life ( $T_{1/2}$ ) of 4.5 minutes in humans, Christofides et al., *Gastroenterology* 76, 903-907 (1979), which makes it necessary to administer the hormone by continuous infusion to induce a therapeutic effect.

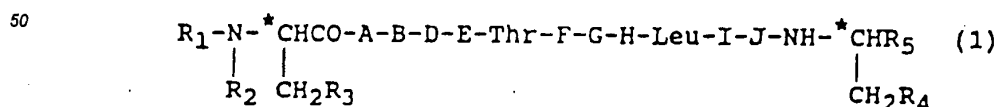
The N-terminal amino acid sequence and certain residues of the mid-portion of motilin are essential for contractile activity, [Macielag et al., *Peptides* 13, 565-569 (1992); Peeters et al., *Peptides* 13, 1103-1107 (1992); Poitras et al., *Biochem. Biophys. Res. Commun.* 183, 36-40 (1992)]. Motilin-like polypeptides which have a shorter C-terminus, contain from 3 to 5 basic amino acids bonded from position 12, and have various amino acid substitutions at positions 1 through 11 have been reported to have activity less than, or equal to, that of motilin.

A motilin antagonist which displaces labeled porcine motilin in rabbit smooth muscle has been reported, "The Motilin Antagonist ANQ-11125 Blocks Erythromycin-Induced Contractions *In Vitro*", Peeters, T.L., Depoortere, I., Macielag, M.J., Dharanipragada, R., Marvin, M.S., Florance, J.R., Vantrappen, G., Galdes, A., *Gastroenterology* 1993, 104, A564.

Although a clear correlation has not been established between hypermotilinemia and disease, elevated plasma motilin levels have been observed in clinical conditions associated with gastrointestinal hypermotility syndromes such as infectious diarrhea and Crohn's disease. This observation suggests that an agent which inhibits the interaction of motilin with its receptor would be useful in the treatment of the disordered intestinal peristalsis associated with these conditions.

In addition, a motilin-like polypeptide having potent gastrointestinal motor inhibitory activity would be useful for the treatment of increased basal levels of gastrointestinal motor activity.

This invention pertains to polypeptides having gastrointestinal motor inhibitory activity represented by the formula:



including optically active isomeric forms and the pharmaceutically acceptable acid addition salts thereof wherein:

A is the L-stereoisomer of a lipophilic aliphatic or alicyclic amino acid;

B is selected from the group consisting of L and D aromatic, heteroaromatic, lipophilic aliphatic, and

alicyclic amino acids;

D is the L-stereoisomer of a lipophilic aliphatic or alicyclic amino acid;

E is the L-stereoisomer of an aromatic, aliphatic, or alicyclic amino acid;

F is the L-stereoisomer of an aromatic or heteroaromatic amino acid;

5 G is glycine or D-alanine;

H is L-glutamic acid or L-glutamine;

I is L-glutamine, L-glutamic acid, or L-alanine;

J is a direct bond between I and group -NH- or is selected from the group consisting of Z, Z-Leu, Z-Leu-Gln, Z-Leu-Gln-Glu, Z-Leu-Gln-Glu-Lys, Z-Leu-Gln-Glu-Lys-Glu, Z-Leu-Gln-Glu-Lys-Glu-Arg, Z-Leu-Gln-Glu-Lys-Glu-Arg-Asn, Z-Leu-Gln-Glu-Lys-Glu-Arg-Asn-Lys, and Z-Leu-Gln-Glu-Lys-Glu-Arg-Asn-Lys-Gly, wherein Z is selected from the group consisting of arginine, D-arginine, D-homoarginine, D-lysine, D-ornithine, D-2,4-diaminobutyric acid, D-glutamine, D-asparagine, and D-alanine;

R<sub>1</sub> and R<sub>2</sub> are independently hydrogen or lower-alkyl;

15 R<sub>3</sub> is selected from the group consisting of lower-alkyl, cycloalkyl, substituted and unsubstituted aryl, and heteroaryl, wherein the aryl group may be substituted with one or more substituents selected from the group consisting of halogen, hydroxy, and lower-alkoxy;

R<sub>4</sub> is selected from the group consisting of -CH<sub>2</sub>CONH<sub>2</sub>, aminoalkyl groups containing from 1 to 3 carbon atoms, and guanidinoalkyl groups containing 2 or 3 carbon atoms;

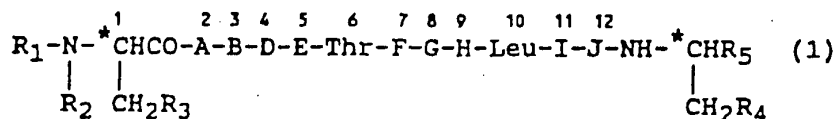
R<sub>5</sub> is -COOH or -CONH<sub>2</sub>; and

20 the symbol \* represents an asymmetric carbon atom which may be in the D or L configuration, and each lower-alkyl group contains from 1 to 4 carbon atoms, with the proviso that R<sub>4</sub> is -CH<sub>2</sub>CONH<sub>2</sub> only when J is Z-Leu or Z-Leu-Gln-Glu-Lys-Glu-Arg-Asn-Lys-Gly.

The novel polypeptides of the present invention are distinct from motilin and yet inhibit the interaction of motilin with its receptor thereby preventing the peristaltic effects of the hormone on gastrointestinal tissue.

25 The motilin-like polypeptides contain an aromatic, heteroaromatic, lipophilic aliphatic, or alicyclic amino acid residue, which is preferably D-phenylalanine or L-phenylalanine, in place of proline at position 3 to inhibit the interaction of motilin with its receptor. The polypeptides of the present invention are therefore useful as investigative tools for probing membrane-bound motilin receptors and are useful in the treatment of conditions characterized by a increased basal level of gastrointestinal motor activity such as infectious diarrhea and Crohn's disease.

30 This invention pertains to novel polypeptides having potent gastrointestinal motor inhibitory activity as well as to methods for treating a condition of increased basal level of gastrointestinal motor activity in a mammal, particularly a human. The methods comprise administering to the mammal an amount, therapeutically effective to relieve such condition, of a polypeptide represented by formula (1):



40 including optically active isomeric forms and the pharmaceutically acceptable acid addition salts thereof. In formula (1), the symbol \* represents an asymmetric carbon atom which may be in the D or L configuration, and each lower-alkyl group contains from 1 to 4 carbon atoms, providing that R<sub>4</sub> is -CH<sub>2</sub>CONH<sub>2</sub> only when J is Z-Leu or Z-Leu-Gln-Glu-Lys-Glu-Arg-Asn-Lys-Gly. Groups A through J and R<sub>1</sub> through R<sub>5</sub> are defined as set forth below.

45 The novel compounds of the present invention defined by Formula (1) are polypeptides which may be from 12 to 22 amino acids in length, and preferably are 12, 14, 16, 18, 20, or 22 amino acids in length. The stereochemistry of the constituent amino acids of the novel polypeptides is an essential feature of this invention. The absolute stereochemistry of the individual amino acids is L, unless otherwise noted, except for position 1 (the amino-terminal amino acid, (R<sub>1</sub>)<sub>m</sub>(R<sub>2</sub>)(R<sub>3</sub>)N-<sup>\*</sup>CH(CH<sub>2</sub>R<sub>4</sub>)CO-) which may be L or D, position 3 (Group B) which may be of L or D, position 8 (Group G) which may be glycine or D-alanine, position 12 which may be L or D, and the C-terminal amino acid position, -NH-<sup>\*</sup>CH(CH<sub>2</sub>R<sub>4</sub>)R<sub>5</sub>, which may be L or D.

The following abbreviations employed throughout this specification are defined as set forth below:

55 Phe - phenylalanine  
Tyr- tyrosine  
Nle - norleucine  
Leu - leucine

- Cha -  $\beta$ -cyclohexylalanine  
 Val - valine  
 Ile - isoleucine  
 Gly - glycine  
 5 Ala - alanine  
 Glu - glutamic acid  
 Gln - glutamine  
 Arg - arginine  
 h-Arg - homoarginine  
 10 Orn - ornithine  
 Dab - 2,4-diaminobutyric acid  
 Lys - lysine  
 Asn - asparagine  
 Me - methyl  
 15 Boc - *t*-butyloxycarbonyl  
 Cbz- benzyloxycarbonyl  
 Dhbt - 3,4-dihydro-4-oxobenzotriazin-3-yl  
 Fmoc - fluorenylmethyloxycarbonyl  
 Mbh - 4,4'-dimethoxybenzhydryl  
 20 Mtr - 4-methoxy-2,3,6-trimethylbenzenesulfonyl  
 Pfp - pentafluorophenyl  
 Trt - trityl  
 BOP- benzotriazolyloxy-trisdimethylaminophosphonium hexafluorophosphate  
 DCC - N',N'-dicyclohexylcarbodiimide  
 25 DCM - dichloromethane  
 DIC - diisopropylcarbodiimide  
 DIEA - diisopropylethylamine  
 EDCC - N-diethylaminopropyl-N'-cyclohexylcarbodiimide  
 HBTU - 2-(1H-benzotriazol-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate  
 30 HEPES - (N-[2-hydroxyethyl]piperazine-N'-[2-ethanesulfonic acid])  
 HMPA - hydroxymethylphenoxyacetoxyl  
 HOBt - 1-hydroxybenzotriazole  
 MBHA - 4-methylbenzhydrylamino  
 PAM - hydroxymethylphenylacetamidomethyl  
 35 PyBOP - bromo-tris-pyrrolidino-phosphonium hexafluorophosphate  
 DMF - N,N-dimethylformamide  
 NMM - N-methylmorpholine  
 NMP - N-methylpyrrolidinone  
 TCA - trichloroacetic acid  
 40 TEA - triethylamine  
 TFA - trifluoroacetic acid  
 TFMSA - trifluoromethanesulfonic acid

45 **Position 1, the amino-terminal amino acid,**



The amino acid in the amino-terminal portion of the polypeptide,  $(R_1)(R_2)N-CH(CH_2R_3)CO-$ , in position 1 may have the L or D configuration.  $R_1$  and  $R_2$  may be independently selected from the group consisting of hydrogen and lower-alkyl. The amino-terminal portion may be unsubstituted, in which case  $R_1$  and  $R_2$  are hydrogen. The term "lower-alkyl", as used herein, refers to straight- and branched-chain hydrocarbon radicals containing from 1 to 4 carbon atoms. Examples of suitable lower-alkyl groups for  $R_1$  and  $R_2$  are methyl, ethyl, propyl, isopropyl, butyl, isobutyl, and *sec*-butyl, preferably methyl. Preferably, the amino-terminal amino acid is N-substituted, and the preferred substituents are one or two methyl groups.

55  $R_3$  is selected from the group consisting of lower-alkyl, cycloalkyl, substituted and unsubstituted aryl, and heteroaryl, wherein the aryl group may contain one or more substituents selected from the group consisting of halogen, hydroxy, and lower-alkoxy. Preferred substituted and unsubstituted aryl groups are phenyl, *p*-fluorophenyl, *p*-chlorophenyl, *p*-bromophenyl, *p*-iodophenyl, *p*-hydroxyphenyl, *p*-methoxyphenyl, 1-naphthyl, and

2-naphthyl. Preferred heteroaryl groups are 3-indolyl, 2-thienyl, and 3-pyridyl. Preferred cycloalkyl groups are cyclopentyl, cyclohexyl, and cycloheptyl. Preferably,  $R_3$  is selected from the group consisting of methyl, ethyl, *n*-propyl, *iso*-propyl, *n*-butyl, cyclohexyl, phenyl, *p*-fluorophenyl, *p*-chlorophenyl, *p*-bromophenyl, *p*-iodophenyl, *p*-hydroxyphenyl, *p*-methoxyphenyl, 1-naphthyl, 2-naphthyl, 3-indolyl, 2-thienyl, and 3-pyridyl. More preferably,  $R_3$  is selected from the group consisting of phenyl and cyclohexyl. Examples of the amino acid residues from which  $(R_1)(R_2)N^*CH(CH_2R_3)CO-$  may be derived are phenylalanine, *p*-fluorophenylalanine, *p*-chlorophenylalanine, *p*-bromophenylalanine, *p*-iodophenylalanine, tyrosine, *p*-methoxyphenylalanine, 1-naphthylalanine, 2-naphthylalanine, tryptophan,  $\beta$ -2-thienylalanine,  $\beta$ -3-pyridylalanine,  $\alpha$ -aminobutyric acid, norvaline, norleucine, leucine, and cyclohexylalanine. For compounds having high levels of gastrointestinal antiperistaltic activity, the preferred amino-terminal amino acids are L-phenylalanine, D-phenylalanine, L-cyclohexylalanine, and D-cyclohexylalanine.

#### Position 2, Group A

Group A in position 2 of the polypeptide is an amino acid which is the L-stereoisomer of a lipophilic aliphatic or alicyclic amino acid such as valine, isoleucine, leucine, norvaline, norleucine, and cyclohexylalanine. The preferred Group A amino acids are L-valine, L-leucine, and L-isoleucine.

#### Position 3, Group B

Group B in position 3 is an amino acid which may be of the L or D configuration and is any of several aromatic, heteroaromatic, lipophilic aliphatic, and alicyclic amino acid residues. These amino acid residues may be derived from the group including phenylalanine, *p*-fluorophenylalanine, *p*-chlorophenylalanine, *p*-bromophenylalanine, *p*-iodophenylalanine, tyrosine, *p*-methoxyphenylalanine, 1-naphthylalanine, 2-naphthylalanine, tryptophan,  $\beta$ -2-thienylalanine,  $\beta$ -3-pyridylalanine,  $\alpha$ -aminobutyric acid, norvaline, norleucine, leucine, and cyclohexylalanine. For compounds having high levels of motilin receptor antagonist activity, the preferred Group B amino acids are D-phenylalanine and L-phenylalanine. In the definition of Group B, proline and alanine are not included within lipophilic aliphatic amino acids. Proline and alanine in position 3 do not yield polypeptides having antagonist activity.

#### Position 4, Group D

Group D in position 4 is an amino acid which is the L-stereoisomer of a lipophilic aliphatic or alicyclic amino acid such as isoleucine, valine, leucine, norvaline, norleucine, and cyclohexylalanine. The preferred Group D amino acids are L-isoleucine, L-leucine, and L-cyclohexylalanine.

#### Position 5, Group E

Group E in position 5 is an amino acid which is the L-stereoisomer of an aromatic, aliphatic, or alicyclic amino acid such as phenylalanine, *p*-fluorophenylalanine, *p*-chlorophenylalanine, *p*-bromophenylalanine, *p*-iodophenylalanine, tyrosine, *p*-methoxyphenylalanine, 1-naphthylalanine, 2-naphthylalanine, leucine, alanine, and cyclohexylalanine. The preferred Group E amino acids are L-phenylalanine, L-alanine, and L-cyclohexylalanine.

#### Position 6, L-threonine

The amino acid in position 6 is L-threonine.

#### Position 7, Group F

Group F in position 7 is an amino acid which is the L-stereoisomer of an aromatic or heteroaromatic amino acid such as tyrosine, phenylalanine, *p*-methoxyphenylalanine, histidine, tryptophan,  $\beta$ -2-thienylalanine, and  $\beta$ -3-pyridylalanine. The preferred Group F amino acids are L-tyrosine, L-histidine, and L-phenylalanine.

#### Position 8, Group G

Group G in position 8 is an amino acid which is glycine or D-alanine, preferably glycine.

**Position 9, Group H**

Group H in position 9 is an amino acid which L-glutamic acid or L-glutamine, preferably L-glutamic acid.

**5 Position 10, L-leucine**

The amino acid in position 10 is L-leucine.

**Position 11, Group I**

10

Group I in position 11 is an amino acid which is L-glutamine, L-glutamic acid, or L-alanine, preferably L-glutamine and L-alanine.

**Group J**

15

Group J may be a direct bond between Group I and the -NH- group or may be selected from the group consisting of Z, Z-Leu, Z-Leu-Gln, Z-Leu-Gln-Glu, Z-Leu-Gln-Glu-Lys, Z-Leu-Gln-Glu-Lys-Glu, Z-Leu-Gln-Glu-Lys-Glu-Arg, Z-Leu-Gln-Glu-Lys-Glu-Arg-Asn, Z-Leu-Gln-Glu-Lys-Glu-Arg-Asn-Lys, and Z-Leu-Gln-Glu-Lys-Glu-Arg-Asn-Lys-Gly, and preferably from the group consisting of Z-Leu, Z-Leu-Gln-Glu, Z-Leu-Gln-Glu-Lys-Glu, Z-Leu-Gln-Glu-Lys-Glu-Arg-Asn, and Z-Leu-Gln-Glu-Lys-Glu-Arg-Asn-Lys-Gly. Group Z is an amino acid selected from the group consisting of arginine, D-arginine, D-homoarginine, D-lysine, D-ornithine, D-2,4-diaminobutyric acid, D-glutamine, D-asparagine, and D-alanine, preferably selected from the group consisting of arginine, D-arginine, D-glutamine, and D-alanine.

**25 Position 12**

When Group J is a direct bond between Group I and the -NH- group, the polypeptide is a dodecapeptide and the amino acid in position 12 is the C-terminal portion,  $-\text{NH}^*\text{CH}(\text{CH}_2\text{R}_4)-\text{R}_5$ , of the polypeptide wherein  $\text{R}_4$  is an aminoalkyl group containing from 1 to 3 carbon atoms or a guanidinoalkyl group containing 2 or 3 carbon atoms, preferably the latter. Preferred aminoalkyl groups are aminomethyl, 2-aminoethyl, and 3-amino-n-propyl. Preferred guanidinoalkyl groups are N-2-guanidinoethyl and N-3-guanidino-n-propyl. Group  $\text{R}_5$  is  $-\text{COOH}$  or  $\text{CONH}_2$ , preferably  $-\text{CONH}_2$ . Preferably, the amino acid in the C-terminal portion,  $-\text{NH}^*\text{CH}(\text{CH}_2\text{R}_4)-\text{R}_5$ , of the polypeptide in this embodiment is selected from the group consisting of arginine, D-arginine, lysine, D-lysine, D-ornithine, D-2,4-diaminobutyric acid, and D-homoarginine, and more preferably is selected from the group consisting of arginine, D-arginine, lysine, and D-lysine.

When Group J is not a direct bond between Group I and the -NH- group, the amino acid in position 12 is Group Z, as defined above.

**Position 13**

40

When the polypeptide in the present invention is a tridecapeptide, the amino acid in position 13 is the C-terminal portion,  $-\text{NH}^*\text{CH}(\text{CH}_2\text{R}_4)-\text{R}_5$ , of the polypeptide, may have the L or D configuration, and may be selected from the group consisting of lysine, ornithine, 2,4-diaminobutyric acid, arginine, and homoarginine, preferably L-lysine or D-lysine.

45 When the polypeptide of the present invention is larger than a tridecapeptide, the amino acid in position 13 is L-leucine.

**Position 14**

50 When the polypeptide in the present invention is a tetradecapeptide, the amino acid in position 14 is the C-terminal portion,  $-\text{NH}^*\text{CH}(\text{CH}_2\text{R}_4)-\text{R}_5$ , of the polypeptide, may have the L or D configuration, and may be selected from the group consisting of glutamine, lysine, ornithine, 2,4-diaminobutyric acid, arginine, and homoarginine, and preferably is selected from the group consisting of L-lysine, D-lysine, L-glutamine, and D-glutamine.

55 When the polypeptide of the present invention is larger than a tetradecapeptide, the amino acid in position 14 of the polypeptide is L-glutamine.

**Position 15**

When the polypeptide is a pentadecapeptide, the amino acid in position 15 is the C-terminal portion,  $\text{-NH-}^*\text{CH}(\text{CH}_2\text{R}_4)\text{-R}_5$ , of the polypeptide, may have the L or D configuration, and may be selected from the group consisting of lysine, ornithine, 2,4-diaminobutyric acid, arginine, and homoarginine, preferably L-lysine or D-lysine.

When the polypeptide of the present invention is larger than a pentadecapeptide, the amino acid in position 15 is L-glutamic acid.

**Position 16**

When the polypeptide is a hexadecapeptide, the amino acid in position 16 is the C-terminal portion,  $\text{-NH-}^*\text{CH}(\text{CH}_2\text{R}_4)\text{-R}_6$ , of the polypeptide, may have the L or D configuration, and may be selected from the group consisting of lysine, ornithine, 2,4-diaminobutyric acid, arginine, and homoarginine, preferably L-lysine or D-lysine.

When the polypeptide of the present invention is larger than a hexadecapeptide, the amino acid in position 16 of the polypeptide is L-lysine.

**Position 17**

When the polypeptide is a heptadecapeptide, the amino acid in position 17 is the C-terminal portion,  $\text{-NH-}^*\text{CH}(\text{CH}_2\text{R}_4)\text{-R}_6$ , of the polypeptide, may have the L or D configuration, and may be selected from the group consisting of lysine, ornithine, 2,4-diaminobutyric acid, arginine, and homoarginine, preferably L-lysine or D-lysine.

When the polypeptide of the present invention is larger than a heptadecapeptide, the amino acid in position 17 is L-glutamic acid.

**Position 18**

When the polypeptide is an octadecapeptide, the amino acid in position 18 is the C-terminal portion,  $\text{-NH-}^*\text{CH}(\text{CH}_2\text{R}_4)\text{-R}_6$ , of the polypeptide, may have the L or D configuration, and may be selected from the group consisting of lysine, ornithine, 2,4-diaminobutyric acid, arginine, and homoarginine, and preferably is selected from the group consisting of L-lysine D-lysine, L-arginine, and D-arginine.

When the polypeptide of the present invention is larger than an octadecapeptide, the amino acid in position 18 of the polypeptide is L-arginine.

**Position 19**

When the polypeptide is a nonadecapeptide, the amino acid in position 19 is the C-terminal portion,  $\text{-NH-}^*\text{CH}(\text{CH}_2\text{R}_4)\text{-R}_6$ , of the polypeptide, may have the L or D configuration, and may be selected from the group consisting of lysine, ornithine, 2,4-diaminobutyric acid, arginine, and homoarginine, preferably L-lysine or D-lysine.

When the polypeptide of the present invention is larger than a nonadecapeptide, the amino acid in position 19 is L-asparagine.

**Position 20**

When the polypeptide consists of 20 amino acids, the amino acid in position 20 is the C-terminal portion,  $\text{-NH-}^*\text{CH}(\text{CH}_2\text{R}_4)\text{-R}_5$ , of the polypeptide, may have the L or D configuration, and may be selected from the group consisting of lysine, ornithine, 2,4-diaminobutyric acid, arginine, and homoarginine, and preferably is L-lysine or D-lysine.

When the polypeptide of the present invention is larger than 20 amino acids, the amino acid in position 20 of the polypeptide is L-lysine.

**Position 21**

When the polypeptide consists of 21 amino acids, the amino acid in position 21 is the C-terminal portion,  $\text{-NH-}^*\text{CH}(\text{CH}_2\text{R}_4)\text{-R}_5$ , of the polypeptide, may have the L or D configuration, and may be selected from the



group consisting of lysine, ornithine, 2,4-diaminobutyric acid, arginine, and homoarginine, preferably L-lysine or D-lysine.

When the polypeptide of the present invention is larger than 21 amino acids, the amino acid in position 21 is glycine.

5

#### Position 22

The amino acid in position 22 of certain of the polypeptides of this invention is the C-terminal portion, -NH-\*CH(CH<sub>2</sub>R<sub>4</sub>)-R<sub>5</sub>, of the polypeptide, may have the L or D configuration, and may be selected from the group consisting of glutamine, lysine, ornithine, 2,4-diaminobutyric acid, arginine, and homoarginine, and preferably is selected from the group consisting of L-lysine, D-lysine, L-glutamine, and D-glutamine.

10

The C-terminal amino acid, -NH-\*CH(CH<sub>2</sub>R<sub>4</sub>)R<sub>5</sub>,

The residue present in the C-terminal position, -NH-\*CH(CH<sub>2</sub>R<sub>4</sub>)-R<sub>5</sub>, of the polypeptides of this invention is an amino acid with a C-terminal carboxylic acid derivative R<sub>5</sub>, wherein R<sub>5</sub> is -COOH or -CONH<sub>2</sub>, preferably -CONH<sub>2</sub>. R<sub>4</sub> is as defined above.

15

The term "cycloalkyl", as used herein, means cyclic hydrocarbon radicals containing from 5 to 7 carbon atoms. Examples of suitable cyclic hydrocarbon radicals are cyclopentyl, cyclohexyl, and cycloheptyl. The term "halogen" as used herein, includes all four halogens with chlorine being preferred.

20

In a preferred embodiment, the compounds of the present invention are selected from the group consisting of:

25 H-Phe-Val-Phe-Ile-Phe-Thr-Tyr-Gly-Glu-Leu-Gln-Arg-Leu-Gln-Lys-Glu-Arg-Asn-Lys-Gly-Gln-OH;  
 H-Phe-Val-Phe-Ile-Phe-Thr-Tyr-Gly-Glu-Leu-Gln-Arg-Leu-Gln-Lys-Glu-Arg-Asn-Lys-Gly-Gln-NH<sub>2</sub>;  
 H-Phe-Val-D-Phe-Ile-Phe-Thr-Tyr-Gly-Glu-Leu-Gln-Arg-Leu-Gln-Lys-Glu-Arg-Asn-Lys-Gly-Gln-OH;  
 H-Phe-Val-D-Phe-Ile-Phe-Thr-Tyr-Gly-Glu-Leu-Gln-Arg-Leu-Gln-Lys-Glu-Arg-Asn-Lys-Gly-Gln-NH<sub>2</sub>;  
 30 H-Phe-Val-Phe-Ile-Phe-Thr-Tyr-Gly-Glu-Leu-Gln-Arg-NH<sub>2</sub>;  
 H-Phe-Val-Phe-Ile-Phe-Thr-Tyr-Gly-Glu-Leu-Gln-Arg-Leu-Gln-OH;  
 (H-Me)-Phe-Val-Phe-Ile-Phe-Thr-Tyr-Gly-Glu-Leu-Gln-Arg-Leu-Gln-OH;  
 35 (Me<sub>2</sub>N)-Phe-Val-Phe-Ile-Phe-Thr-Tyr-Gly-Glu-Leu-Gln-Arg-Leu-Gln-OH;  
 H-Phe-Val-p-I-Phe-Ile-Phe-Thr-Tyr-Gly-Glu-Leu-Gln-Arg-Leu-Gln-OH;  
 H-Phe-Val-Leu-Ile-Phe-Thr-Tyr-Gly-Glu-Leu-Gln-Arg-Leu-Gln-OH;  
 40 H-Phe-Val-Thi-Ile-Phe-Thr-Tyr-Gly-Glu-Leu-Gln-Arg-Leu-Gln-OH;  
 H-Phe-Val-Cha-Ile-Phe-Thr-Tyr-Gly-Glu-Leu-Gln-Arg-Leu-Gln-OH;  
 H-Phe-Val-2-Mal-Ile-Phe-Thr-Tyr-Gly-Glu-Leu-Gln-Arg-Leu-Gln-OH;  
 H-Phe-Val-D-Phe-Ile-Phe-Thr-Tyr-Gly-Glu-Leu-Gln-Arg-Leu-Gln-OH;  
 45 H-Phe-Val-Phe-Leu-Phe-Thr-Tyr-Gly-Glu-Leu-Gln-Arg-Leu-Gln-OH;

50

55

H-Phe-Val-Phe-Ile-Cha-Thr-Tyr-Gly-Glu-Leu-Gln-Arg-Leu-Gln-OH;  
 H-Phe-Val-Phe-Ile-Ala-Thr-Tyr-Gly-Glu-Leu-Gln-Arg-Leu-Gln-OH;  
 H-Phe-Val-Phe-Ile-Phe-Thr-Phe-Gly-Glu-Leu-Gln-Arg-Leu-Gln-OH;  
 5 H-Phe-Val-Phe-Ile-Phe-Thr-Tyr-D-Ala-Glu-Leu-Gln-Arg-Leu-Gln-OH;  
 H-Phe-Val-Phe-Ile-Phe-Thr-Tyr-Gly-Gln-Leu-Gln-Arg-Leu-Gln-OH;  
 H-Phe-Val-Phe-Ile-Phe-Thr-Tyr-Gly-Glu-Leu-Ala-Arg-Leu-Gln-OH;  
 10 H-Phe-Leu-Phe-Ile-Phe-Thr-Tyr-Gly-Glu-Leu-Gln-Arg-Leu-Gln-OH;  
 H-Phe-Val-Phe-Ile-Phe-Thr-Tyr-Gly-Glu-Leu-Gln-Arg-Leu-Gln-NH<sub>2</sub>;  
 (N-Me)-Phe-Val-Phe-Ile-Phe-Thr-Tyr-Gly-Glu-Leu-Gln-Arg-Leu-Gln-NH<sub>2</sub>;  
 (Me<sub>2</sub>N)-Phe-Val-Phe-Ile-Phe-Thr-Tyr-Gly-Glu-Leu-Gln-Arg-Leu-Gln-NH<sub>2</sub>;  
 15 H-Phe-Val-p-I-Phe-Ile-Phe-Thr-Tyr-Gly-Glu-Leu-Gln-Arg-Leu-Gln-NH<sub>2</sub>;  
 H-Phe-Val-Leu-Ile-Phe-Thr-Tyr-Gly-Glu-Leu-Gln-Arg-Leu-Gln-NH<sub>2</sub>;  
 H-Phe-Val-Thi-Ile-Phe-Thr-Tyr-Gly-Glu-Leu-Gln-Arg-Leu-Gln-NH<sub>2</sub>;  
 20 H-Phe-Val-Cha-Ile-Phe-Thr-Tyr-Gly-Glu-Leu-Gln-Arg-Leu-Gln-NH<sub>2</sub>;  
 H-Phe-Val-2-Nal-Ile-Phe-Thr-Tyr-Gly-Glu-Leu-Gln-Arg-Leu-Gln-NH<sub>2</sub>;  
 H-Phe-Val-D-Phe-Ile-Phe-Thr-Tyr-Gly-Glu-Leu-Gln-Arg-Leu-Gln-NH<sub>2</sub>;  
 25 H-Phe-Val-Phe-Leu-Phe-Thr-Tyr-Gly-Glu-Leu-Gln-Arg-Leu-Gln-NH<sub>2</sub>;  
 H-Phe-Val-Phe-Ile-Cha-Thr-Tyr-Gly-Glu-Leu-Gln-Arg-Leu-Gln-NH<sub>2</sub>;  
 H-Phe-Val-Phe-Ile-Ala-Thr-Tyr-Gly-Glu-Leu-Gln-Arg-Leu-Gln-NH<sub>2</sub>;  
 H-Phe-Val-Phe-Ile-Phe-Thr-Phe-Gly-Glu-Leu-Gln-Arg-Leu-Gln-NH<sub>2</sub>;  
 30 H-Phe-Val-Phe-Ile-Phe-Thr-Tyr-D-Ala-Glu-Leu-Gln-Arg-Leu-Gln-NH<sub>2</sub>;  
 H-Phe-Val-Phe-Ile-Phe-Thr-Tyr-Gly-Gln-Leu-Gln-Arg-Leu-Gln-NH<sub>2</sub>;  
 H-Phe-Val-Phe-Ile-Phe-Thr-Tyr-Gly-Glu-Leu-Ala-Arg-Leu-Gln-NH<sub>2</sub>;  
 35 H-Phe-Leu-Phe-Ile-Phe-Thr-Tyr-Gly-Glu-Leu-Gln-Arg-Leu-Gln-NH<sub>2</sub>;  
 H-Phe-Val-Phe-Ile-Phe-Thr-Tyr-Gly-Glu-Leu-Gln-Arg-Leu-Lys-NH<sub>2</sub>;  
 H-D-Phe-Val-Phe-Ile-Phe-Thr-Tyr-Gly-Glu-Leu-Gln-Arg-Leu-Gln-OH;  
 40 H-Cha-Val-Phe-Ile-Phe-Thr-Tyr-Gly-Glu-Leu-Gln-Arg-Leu-Gln-OH;  
 H-Phe-Val-Pal-Ile-Phe-Thr-Tyr-Gly-Glu-Leu-Gln-Arg-Leu-Gln-OH;  
 H-D-Phe-Val-Phe-Ile-Phe-Thr-Tyr-Gly-Glu-Leu-Gln-Arg-Leu-Gln-NH<sub>2</sub>;  
 H-Cha-Val-Phe-Ile-Phe-Thr-Tyr-Gly-Glu-Leu-Gln-Arg-Leu-Gln-NH<sub>2</sub>;  
 45 H-Phe-Val-Pal-Ile-Phe-Thr-Tyr-Gly-Glu-Leu-Gln-Arg-Leu-Gln-NH<sub>2</sub>;  
 H-Phe-Val-Phe-Ile-Phe-Thr-Tyr-Gly-Glu-Leu-Gln-Arg-Leu-D-Gln-NH<sub>2</sub>;  
 H-Phe-Val-D-Phe-Ile-Phe-Thr-Tyr-Gly-Glu-Leu-Gln-Arg-NH<sub>2</sub>;  
 50 H-Phe-Val-D-Phe-Ile-Phe-Thr-Tyr-Gly-Glu-Leu-Gln-Arg-Leu-Gln-OH;  
 (N-Me)-Phe-Val-D-Phe-Ile-Phe-Thr-Tyr-Gly-Glu-Leu-Gln-Arg-Leu-Gln-OH;  
 (Me<sub>2</sub>N)-Phe-Val-D-Phe-Ile-Phe-Thr-Tyr-Gly-Glu-Leu-Gln-Arg-Leu-Gln-OH;  
 55 H-Phe-Val-D-Phe-Leu-Phe-Thr-Tyr-Gly-Glu-Leu-Gln-Arg-Leu-Gln-OH;  
 H-Phe-Val-D-Phe-Ile-Cha-Thr-Tyr-Gly-Glu-Leu-Gln-Arg-Leu-Gln-OH;  
 H-Phe-Val-D-Phe-Ile-Ala-Thr-Tyr-Gly-Glu-Leu-Gln-Arg-Leu-Gln-OH;

H-Phe-Val-D-Phe-Ile-Phe-Thr-Phe-Gly-Glu-Leu-Gln-Arg-Leu-Gln-OH;  
 H-Phe-Val-D-Phe-Ile-Phe-Thr-Tyr-D-Ala-Glu-Leu-Gln-Arg-Leu-Gln-OH;  
 H-Phe-Val-D-Phe-Ile-Phe-Thr-Tyr-Gly-Gln-Leu-Gln-Arg-Leu-Gln-OH;  
 5 H-Phe-Val-D-Phe-Ile-Phe-Thr-Tyr-Gly-Glu-Leu-Ala-Arg-Leu-Gln-OH;  
 H-Phe-Leu-D-Phe-Ile-Phe-Thr-Tyr-Gly-Glu-Leu-Gln-Arg-Leu-Gln-OH;  
 H-Phe-Val-D-Phe-Ile-Phe-Thr-Tyr-Gly-Glu-Leu-Gln-Arg-Leu-Gln-NH<sub>2</sub>;  
 10 (N-Me)-Phe-Val-D-Phe-Ile-Phe-Thr-Tyr-Gly-Glu-Leu-Gln-Arg-Leu-Gln-NH<sub>2</sub>;  
 (Me<sub>2</sub>N)-Phe-Val-D-Phe-Ile-Phe-Thr-Tyr-Gly-Glu-Leu-Gln-Arg-Leu-Gln-NH<sub>2</sub>;  
 H-Phe-Val-D-Phe-Leu-Phe-Thr-Tyr-Gly-Glu-Leu-Gln-Arg-Leu-Gln-NH<sub>2</sub>;  
 H-Phe-Val-D-Phe-Ile-Cha-Thr-Tyr-Gly-Glu-Leu-Gln-Arg-Leu-Gln-NH<sub>2</sub>;  
 15 H-Phe-Val-D-Phe-Ile-Ala-Thr-Tyr-Gly-Glu-Leu-Gln-Arg-Leu-Gln-NH<sub>2</sub>;  
 H-Phe-Val-D-Phe-Ile-Phe-Thr-Phe-Gly-Glu-Leu-Gln-Arg-Leu-Gln-NH<sub>2</sub>;  
 H-Phe-Val-D-Phe-Ile-Phe-Thr-Tyr-D-Ala-Glu-Leu-Gln-Arg-Leu-Gln-NH<sub>2</sub>;  
 20 H-Phe-Val-D-Phe-Ile-Phe-Thr-Tyr-Gly-Gln-Leu-Gln-Arg-Leu-Gln-NH<sub>2</sub>;  
 H-Phe-Val-D-Phe-Ile-Phe-Thr-Tyr-Gly-Glu-Leu-Ala-Arg-Leu-Gln-NH<sub>2</sub>;  
 H-Phe-Leu-D-Phe-Ile-Phe-Thr-Tyr-Gly-Glu-Leu-Gln-Arg-Leu-Gln-NH<sub>2</sub>;  
 25 H-Phe-Val-D-Phe-Ile-Phe-Thr-Tyr-Gly-Glu-Leu-Gln-Arg-Leu-Lys-NH<sub>2</sub>;  
 H-D-Phe-Val-D-Phe-Ile-Phe-Thr-Tyr-Gly-Glu-Leu-Gln-Arg-Leu-Gln-OH;  
 H-Cha-Val-D-Phe-Ile-Phe-Thr-Tyr-Gly-Glu-Leu-Gln-Arg-Leu-Gln-OH;  
 H-Phe-Val-Pal-Ile-Phe-Thr-Tyr-Gly-Glu-Leu-Gln-Arg-Leu-Gln-OH;  
 30 H-D-Phe-Val-D-Phe-Ile-Phe-Thr-Tyr-Gly-Glu-Leu-Gln-Arg-Leu-Gln-NH<sub>2</sub>;  
 H-Cha-Val-D-Phe-Ile-Phe-Thr-Tyr-Gly-Glu-Leu-Gln-Arg-Leu-Gln-NH<sub>2</sub>;  
 H-Phe-Val-Pal-Ile-Phe-Thr-Tyr-Gly-Glu-Leu-Gln-Arg-Leu-Gln-NH<sub>2</sub>;  
 35 H-Phe-Val-D-Phe-Ile-Phe-Thr-Tyr-Gly-Glu-Leu-Gln-Arg-Leu-D-Gln-NH<sub>2</sub>;  
 (N-Me)-Phe-Val-D-Phe-Ile-Phe-Thr-Tyr-Gly-Glu-Leu-Gln-Arg-Leu-D-Gln-NH<sub>2</sub>;  
 (Me<sub>2</sub>N)-Phe-Val-D-Phe-Ile-Phe-Thr-Tyr-Gly-Glu-Leu-Gln-Arg-Leu-D-Gln-NH<sub>2</sub>;  
 40 (N-Me)-Phe-Val-Phe-Ile-Phe-Thr-Tyr-Gly-Glu-Leu-Gln-Arg-Leu-D-Gln-NH<sub>2</sub>;  
 (Me<sub>2</sub>N)-Phe-Val-Phe-Ile-Phe-Thr-Tyr-Gly-Glu-Leu-Gln-Arg-Leu-D-Gln-NH<sub>2</sub>;  
 (N-Me)-Phe-Val-D-Phe-Ile-Phe-Thr-Tyr-Gly-Glu-Leu-Gln-D-Arg-Leu-Gln-NH<sub>2</sub>;  
 (Me<sub>2</sub>N)-Phe-Val-D-Phe-Ile-Phe-Thr-Tyr-Gly-Glu-Leu-Gln-D-Arg-Leu-Gln-NH<sub>2</sub>;  
 45 (N-Me)-Phe-Val-Phe-Ile-Phe-Thr-Tyr-Gly-Glu-Leu-Gln-D-Arg-Leu-Gln-NH<sub>2</sub>;  
 (Me<sub>2</sub>N)-Phe-Val-Phe-Ile-Phe-Thr-Tyr-Gly-Glu-Leu-Gln-D-Arg-Leu-Gln-NH<sub>2</sub>;  
 (N-Me)-Phe-Val-D-Phe-Ile-Phe-Thr-Tyr-Gly-Glu-Leu-Gln-Arg-Leu-Lys-NH<sub>2</sub>;  
 50 (Me<sub>2</sub>N)-Phe-Val-D-Phe-Ile-Phe-Thr-Tyr-Gly-Glu-Leu-Gln-Arg-Leu-Lys-NH<sub>2</sub>;  
 (N-Me)-Phe-Val-Phe-Ile-Phe-Thr-Tyr-Gly-Glu-Leu-Gln-Arg-Leu-Lys-NH<sub>2</sub>;  
 (Me<sub>2</sub>N)-Phe-Val-Phe-Ile-Phe-Thr-Tyr-Gly-Glu-Leu-Gln-Arg-Leu-Lys-NH<sub>2</sub>;  
 55 (N-Me)-Phe-Val-D-Phe-Ile-Phe-Thr-Tyr-Gly-Glu-Leu-Gln-D-Arg-Leu-Lys-NH<sub>2</sub>;  
 (Me<sub>2</sub>N)-Phe-Val-D-Phe-Ile-Phe-Thr-Tyr-Gly-Glu-Leu-Gln-D-Arg-Leu-Lys-NH<sub>2</sub>;  
 (N-Me)-Phe-Val-Phe-Ile-Phe-Thr-Tyr-Gly-Glu-Leu-Gln-D-Arg-Leu-Lys-NH<sub>2</sub>;

(Me<sub>2</sub>N)-Phe-Val-Phe-Ile-Phe-Thr-Tyr-Gly-Glu-Leu-Gln-D-Arg-Leu-Lys-NH<sub>2</sub>;  
 (N-Me)-Phe-Val-D-Phe-Ile-Phe-Thr-Tyr-Gly-Glu-Leu-Gln-Arg-Leu-D-Lys-NH<sub>2</sub>;  
 (Me<sub>2</sub>N)-Phe-Val-D-Phe-Ile-Phe-Thr-Tyr-Gly-Glu-Leu-Gln-Arg-Leu-D-Lys-NH<sub>2</sub>;  
 5 (N-Me)-Phe-Val-Phe-Ile-Phe-Thr-Tyr-Gly-Glu-Leu-Gln-Arg-Leu-D-Lys-NH<sub>2</sub>;  
 (Me<sub>2</sub>N)-Phe-Val-Phe-Ile-Phe-Thr-Tyr-Gly-Glu-Leu-Gln-Arg-Leu-D-Lys-NH<sub>2</sub>;  
 (N-Me)-Phe-Val-D-Phe-Ile-Phe-Thr-Tyr-Gly-Glu-Leu-Gln-D-Arg-Leu-D-Lys-NH<sub>2</sub>;  
 10 (Me<sub>2</sub>N)-Phe-Val-D-Phe-Ile-Phe-Thr-Tyr-Gly-Glu-Leu-Gln-D-Arg-Leu-D-Lys-NH<sub>2</sub>;  
 (N-Me)-Phe-Val-Phe-Ile-Phe-Thr-Tyr-Gly-Glu-Leu-Gln-D-Arg-Leu-D-Lys-NH<sub>2</sub>;  
 (Me<sub>2</sub>N)-Phe-Val-Phe-Ile-Phe-Thr-Tyr-Gly-Glu-Leu-Gln-D-Arg-Leu-D-Lys-NH<sub>2</sub>;  
 (N-Me)-Phe-Val-D-Phe-Ile-Phe-Thr-Tyr-Gly-Glu-Leu-Gln-D-Arg-Leu-D-Gln-NH<sub>2</sub>;  
 15 (Me<sub>2</sub>N)-Phe-Val-D-Phe-Ile-Phe-Thr-Tyr-Gly-Glu-Leu-Gln-D-Arg-Leu-D-Gln-NH<sub>2</sub>;  
 (N-Me)-Phe-Val-Phe-Ile-Phe-Thr-Tyr-Gly-Glu-Leu-Gln-D-Arg-Leu-D-Gln-NH<sub>2</sub>;  
 (Me<sub>2</sub>N)-Phe-Val-Phe-Ile-Phe-Thr-Tyr-Gly-Glu-Leu-Gln-D-Arg-Leu-D-Gln-NH<sub>2</sub>;  
 20 (N-Me)-Phe-Val-D-Phe-Ile-Phe-Thr-Tyr-Gly-Glu-Leu-Ala-Arg-Leu-Gln-NH<sub>2</sub>;  
 (Me<sub>2</sub>N)-Phe-Val-D-Phe-Ile-Phe-Thr-Tyr-Gly-Glu-Leu-Ala-Arg-Leu-Gln-NH<sub>2</sub>;  
 (N-Me)-Phe-Val-Phe-Ile-Phe-Thr-Tyr-Gly-Glu-Leu-Ala-Arg-Leu-Gln-NH<sub>2</sub>;  
 25 (Me<sub>2</sub>N)-Phe-Val-Phe-Ile-Phe-Thr-Tyr-Gly-Glu-Leu-Ala-Arg-Leu-Gln-NH<sub>2</sub>;  
 (N-Me)-Phe-Val-D-Phe-Ile-Phe-Thr-Tyr-Gly-Glu-Leu-Ala-Arg-Leu-D-Gln-NH<sub>2</sub>;  
 (Me<sub>2</sub>N)-Phe-Val-D-Phe-Ile-Phe-Thr-Tyr-Gly-Glu-Leu-Ala-Arg-Leu-D-Gln-NH<sub>2</sub>;  
 (N-Me)-Phe-Val-Phe-Ile-Phe-Thr-Tyr-Gly-Glu-Leu-Ala-Arg-Leu-D-Gln-NH<sub>2</sub>;  
 30 (Me<sub>2</sub>N)-Phe-Val-Phe-Ile-Phe-Thr-Tyr-Gly-Glu-Leu-Ala-Arg-Leu-D-Gln-NH<sub>2</sub>;  
 (N-Me)-Phe-Val-D-Phe-Ile-Phe-Thr-Tyr-Gly-Glu-Leu-Ala-D-Arg-Leu-Gln-NH<sub>2</sub>;  
 (Me<sub>2</sub>N)-Phe-Val-D-Phe-Ile-Phe-Thr-Tyr-Gly-Glu-Leu-Ala-D-Arg-Leu-Gln-NH<sub>2</sub>;  
 35 (N-Me)-Phe-Val-Phe-Ile-Phe-Thr-Tyr-Gly-Glu-Leu-Ala-D-Arg-Leu-Gln-NH<sub>2</sub>;  
 (Me<sub>2</sub>N)-Phe-Val-Phe-Ile-Phe-Thr-Tyr-Gly-Glu-Leu-Ala-D-Arg-Leu-Gln-NH<sub>2</sub>;  
 (N-Me)-Phe-Val-D-Phe-Ile-Phe-Thr-Tyr-Gly-Glu-Leu-Ala-D-Arg-Leu-D-Gln-NH<sub>2</sub>;  
 40 (Me<sub>2</sub>N)-Phe-Val-D-Phe-Ile-Phe-Thr-Tyr-Gly-Glu-Leu-Ala-D-Arg-Leu-D-Gln-NH<sub>2</sub>;  
 (N-Me)-Phe-Val-Phe-Ile-Phe-Thr-Tyr-Gly-Glu-Leu-Ala-D-Arg-Leu-D-Gln-NH<sub>2</sub>;  
 (Me<sub>2</sub>N)-Phe-Val-Phe-Ile-Phe-Thr-Tyr-Gly-Glu-Leu-Ala-D-Arg-Leu-D-Gln-NH<sub>2</sub>;  
 (N-Me)-Phe-Val-D-Phe-Ile-Phe-Thr-Tyr-Gly-Glu-Leu-Ala-D-Arg-Leu-Lys-NH<sub>2</sub>;  
 45 (Me<sub>2</sub>N)-Phe-Val-D-Phe-Ile-Phe-Thr-Tyr-Gly-Glu-Leu-Ala-D-Arg-Leu-Lys-NH<sub>2</sub>;  
 (N-Me)-Phe-Val-Phe-Ile-Phe-Thr-Tyr-Gly-Glu-Leu-Ala-D-Arg-Leu-Lys-NH<sub>2</sub>;  
 (Me<sub>2</sub>N)-Phe-Val-Phe-Ile-Phe-Thr-Tyr-Gly-Glu-Leu-Ala-D-Arg-Leu-Lys-NH<sub>2</sub>;  
 50 (N-Me)-Phe-Val-D-Phe-Ile-Phe-Thr-Tyr-Gly-Glu-Leu-Ala-D-Arg-Leu-D-Lys-NH<sub>2</sub>;  
 (Me<sub>2</sub>N)-Phe-Val-D-Phe-Ile-Phe-Thr-Tyr-Gly-Glu-Leu-Ala-D-Arg-Leu-D-Lys-NH<sub>2</sub>;  
 (N-Me)-Phe-Val-Phe-Ile-Phe-Thr-Tyr-Gly-Glu-Leu-Ala-D-Arg-Leu-D-Lys-NH<sub>2</sub>;  
 55 (Me<sub>2</sub>N)-Phe-Val-Phe-Ile-Phe-Thr-Tyr-Gly-Glu-Leu-Ala-D-Arg-Leu-D-Lys-NH<sub>2</sub>;  
 (N-Me)-Phe-Val-D-Phe-Ile-Phe-Thr-Tyr-Gly-Glu-Leu-Gln-Arg-NH<sub>2</sub>;  
 (Me<sub>2</sub>N)-Phe-Val-D-Phe-Ile-Phe-Thr-Tyr-Gly-Glu-Leu-Gln-Arg-NH<sub>2</sub>;

(N-Me)-Phe-Val-Phe-Ile-Phe-Thr-Tyr-Gly-Glu-Leu-Gln-Arg-NH<sub>2</sub>;  
 (Me<sub>2</sub>N)-Phe-Val-Phe-Ile-Phe-Thr-Tyr-Gly-Glu-Leu-Gln-Arg-NH<sub>2</sub>;  
 5 (N-Me)-Phe-Val-D-Phe-Ile-Phe-Thr-Tyr-Gly-Gln-Leu-Ala-Arg-NH<sub>2</sub>;  
 (Me<sub>2</sub>N)-Phe-Val-D-Phe-Ile-Phe-Thr-Tyr-Gly-Gln-Leu-Ala-Arg-NH<sub>2</sub>;  
 (N-Me)-Phe-Val-Phe-Ile-Phe-Thr-Tyr-Gly-Gln-Leu-Ala-Arg-NH<sub>2</sub>;  
 10 (Me<sub>2</sub>N)-Phe-Val-Phe-Ile-Phe-Thr-Tyr-Gly-Gln-Leu-Ala-Arg-NH<sub>2</sub>;  
 (N-Me)-Phe-Val-D-Phe-Ile-Phe-Thr-Tyr-Gly-Glu-Leu-Gln-D-Arg-NH<sub>2</sub>;  
 (Me<sub>2</sub>N)-Phe-Val-D-Phe-Ile-Phe-Thr-Tyr-Gly-Glu-Leu-Gln-D-Arg-NH<sub>2</sub>;  
 (N-Me)-Phe-Val-Phe-Ile-Phe-Thr-Tyr-Gly-Glu-Leu-Gln-D-Arg-NH<sub>2</sub>;  
 15 (Me<sub>2</sub>N)-Phe-Val-Phe-Ile-Phe-Thr-Tyr-Gly-Glu-Leu-Gln-D-Arg-NH<sub>2</sub>;  
 (N-Me)-Phe-Val-D-Phe-Ile-Phe-Thr-Tyr-Gly-Glu-Leu-Ala-D-Arg-NH<sub>2</sub>;  
 (Me<sub>2</sub>N)-Phe-Val-D-Phe-Ile-Phe-Thr-Tyr-Gly-Glu-Leu-Ala-D-Arg-NH<sub>2</sub>;  
 20 (N-Me)-Phe-Val-Phe-Ile-Phe-Thr-Tyr-Gly-Glu-Leu-Ala-D-Arg-NH<sub>2</sub>; and  
 (Me<sub>2</sub>N)-Phe-Val-Phe-Ile-Phe-Thr-Tyr-Gly-Glu-Leu-Ala-D-Arg-NH<sub>2</sub>;

25 and their pharmaceutically acceptable addition salts. In each case, the amino acids have the L-configuration unless otherwise specified. In a more preferred embodiment, the compounds of the present invention are selected from the group consisting of

H-Phe-Val-Phe-Ile-Phe-Thr-Tyr-Gly-Glu-Leu-Gln-Arg-Leu-Gln-Lys-Glu-Arg-Asn-Lys-Gly-Gln-OH;  
 30 H-Phe-Val-Phe-Ile-Phe-Thr-Tyr-Gly-Glu-Leu-Gln-Arg-Leu-Gln-Lys-Glu-Arg-Asn-Lys-Gly-Gln-NH<sub>2</sub>;  
 H-Phe-Val-D-Phe-Ile-Phe-Thr-Tyr-Gly-Glu-Leu-Gln-Arg-Leu-Gln-Lys-Glu-Arg-Asn-Lys-Gly-Gln-OH;  
 H-Phe-Val-D-Phe-Ile-Phe-Thr-Tyr-Gly-Glu-Leu-Gln-Arg-Leu-Gln-Lys-Glu-Arg-Asn-Lys-Gly-Gln-NH<sub>2</sub>;  
 35 H-Phe-Val-Phe-Ile-Phe-Thr-Tyr-Gly-Glu-Leu-Gln-Arg-NH<sub>2</sub>;  
 H-Phe-Val-Phe-Ile-Phe-Thr-Tyr-Gly-Glu-Leu-Gln-Arg-Leu-Gln-OH;  
 (N-Me)-Phe-Val-Phe-Ile-Phe-Thr-Tyr-Gly-Glu-Leu-Gln-Arg-Leu-Gln-OH;  
 (Me<sub>2</sub>N)-Phe-Val-Phe-Ile-Phe-Thr-Tyr-Gly-Glu-Leu-Gln-Arg-Leu-Gln-OH;  
 40 H-Phe-Val-D-Phe-Ile-Phe-Thr-Tyr-Gly-Glu-Leu-Gln-Arg-Leu-Gln-OH;  
 H-Phe-Val-Phe-Ile-Phe-Thr-Tyr-Gly-Glu-Leu-Gln-Arg-Leu-Gln-NH<sub>2</sub>;  
 (N-Me)-Phe-Val-Phe-Ile-Phe-Thr-Tyr-Gly-Glu-Leu-Gln-Arg-Leu-Gln-NH<sub>2</sub>;  
 45 (Me<sub>2</sub>N)-Phe-Val-Phe-Ile-Phe-Thr-Tyr-Gly-Glu-Leu-Gln-Arg-Leu-Gln-NH<sub>2</sub>;  
 H-Phe-Val-Phe-Ile-Phe-Thr-Tyr-Gly-Glu-Leu-Gln-Arg-Leu-Lys-NH<sub>2</sub>;  
 H-Phe-Val-Phe-Ile-Phe-Thr-Tyr-Gly-Glu-Leu-Gln-Arg-Leu-D-Gln-NH<sub>2</sub>;  
 H-Phe-Val-D-Phe-Ile-Phe-Thr-Tyr-Gly-Glu-Leu-Gln-Arg-NH<sub>2</sub>;  
 50 H-Phe-Val-D-Phe-Ile-Phe-Thr-Tyr-Gly-Glu-Leu-Gln-Arg-Leu-Gln-OH;  
 (N-Me)-Phe-Val-D-Phe-Ile-Phe-Thr-Tyr-Gly-Glu-Leu-Gln-Arg-Leu-Gln-OH;  
 (Me<sub>2</sub>N)-Phe-Val-D-Phe-Ile-Phe-Thr-Tyr-Gly-Glu-Leu-Gln-Arg-Leu-Gln-OH;  
 55 H-Phe-Val-D-Phe-Ile-Phe-Thr-Tyr-Gly-Glu-Leu-Gln-Arg-Leu-Gln-NH<sub>2</sub>;

5  
10  
15  
20  
25  
30  
35  
40  
45  
50  
55

(Me<sub>2</sub>N)-Phe-Val-Phe-Ile-Phe-Thr-Tyr-Gly-Glu-Leu-Ala-Arg-Leu-D-Gln-NH<sub>2</sub>;  
 (N-Me)-Phe-Val-D-Phe-Ile-Phe-Thr-Tyr-Gly-Glu-Leu-Ala-D-Arg-Leu-Gln-NH<sub>2</sub>;  
 (Me<sub>2</sub>N)-Phe-Val-D-Phe-Ile-Phe-Thr-Tyr-Gly-Glu-Leu-Ala-D-Arg-Leu-Gln-NH<sub>2</sub>;  
 (N-Me)-Phe-Val-Phe-Ile-Phe-Thr-Tyr-Gly-Glu-Leu-Ala-D-Arg-Leu-Gln-NH<sub>2</sub>;  
 (Me<sub>2</sub>N)-Phe-Val-Phe-Ile-Phe-Thr-Tyr-Gly-Glu-Leu-Ala-D-Arg-Leu-D-Gln-NH<sub>2</sub>;  
 (N-Me)-Phe-Val-D-Phe-Ile-Phe-Thr-Tyr-Gly-Glu-Leu-Ala-D-Arg-Leu-D-Gln-NH<sub>2</sub>;  
 (Me<sub>2</sub>N)-Phe-Val-D-Phe-Ile-Phe-Thr-Tyr-Gly-Glu-Leu-Ala-D-Arg-Leu-D-Gln-NH<sub>2</sub>;  
 (N-Me)-Phe-Val-Phe-Ile-Phe-Thr-Tyr-Gly-Glu-Leu-Ala-D-Arg-Leu-D-Gln-NH<sub>2</sub>;  
 (Me<sub>2</sub>N)-Phe-Val-Phe-Ile-Phe-Thr-Tyr-Gly-Glu-Leu-Ala-D-Arg-Leu-Lys-NH<sub>2</sub>;  
 (N-Me)-Phe-Val-D-Phe-Ile-Phe-Thr-Tyr-Gly-Glu-Leu-Ala-D-Arg-Leu-Lys-NH<sub>2</sub>;  
 (Me<sub>2</sub>N)-Phe-Val-D-Phe-Ile-Phe-Thr-Tyr-Gly-Glu-Leu-Ala-D-Arg-Leu-Lys-NH<sub>2</sub>;  
 (N-Me)-Phe-Val-Phe-Ile-Phe-Thr-Tyr-Gly-Glu-Leu-Ala-D-Arg-Leu-Lys-NH<sub>2</sub>;  
 (Me<sub>2</sub>N)-Phe-Val-Phe-Ile-Phe-Thr-Tyr-Gly-Glu-Leu-Ala-D-Arg-Leu-D-Lys-NH<sub>2</sub>;  
 (N-Me)-Phe-Val-D-Phe-Ile-Phe-Thr-Tyr-Gly-Glu-Leu-Ala-D-Arg-Leu-D-Lys-NH<sub>2</sub>;  
 (Me<sub>2</sub>N)-Phe-Val-D-Phe-Ile-Phe-Thr-Tyr-Gly-Glu-Leu-Ala-D-Arg-Leu-D-Lys-NH<sub>2</sub>;  
 (N-Me)-Phe-Val-Phe-Ile-Phe-Thr-Tyr-Gly-Glu-Leu-Ala-D-Arg-Leu-D-Lys-NH<sub>2</sub>;  
 (Me<sub>2</sub>N)-Phe-Val-Phe-Ile-Phe-Thr-Tyr-Gly-Glu-Leu-Gln-Arg-NH<sub>2</sub>;  
 (N-Me)-Phe-Val-D-Phe-Ile-Phe-Thr-Tyr-Gly-Glu-Leu-Gln-Arg-NH<sub>2</sub>;  
 (Me<sub>2</sub>N)-Phe-Val-Phe-Ile-Phe-Thr-Tyr-Gly-Glu-Leu-Gln-Arg-NH<sub>2</sub>;  
 (N-Me)-Phe-Val-D-Phe-Ile-Phe-Thr-Tyr-Gly-Gln-Leu-Ala-Arg-NH<sub>2</sub>;  
 (Me<sub>2</sub>N)-Phe-Val-D-Phe-Ile-Phe-Thr-Tyr-Gly-Gln-Leu-Ala-Arg-NH<sub>2</sub>;  
 (N-Me)-Phe-Val-Phe-Ile-Phe-Thr-Tyr-Gly-Gln-Leu-Ala-Arg-NH<sub>2</sub>;  
 (Me<sub>2</sub>N)-Phe-Val-Phe-Ile-Phe-Thr-Tyr-Gly-Gln-Leu-Ala-Arg-NH<sub>2</sub>;  
 (N-Me)-Phe-Val-D-Phe-Ile-Phe-Thr-Tyr-Gly-Glu-Leu-Gln-D-Arg-NH<sub>2</sub>;  
 (Me<sub>2</sub>N)-Phe-Val-D-Phe-Ile-Phe-Thr-Tyr-Gly-Glu-Leu-Gln-D-Arg-NH<sub>2</sub>;  
 (N-Me)-Phe-Val-Phe-Ile-Phe-Thr-Tyr-Gly-Glu-Leu-Gln-D-Arg-NH<sub>2</sub>;  
 (Me<sub>2</sub>N)-Phe-Val-Phe-Ile-Phe-Thr-Tyr-Gly-Glu-Leu-Gln-D-Arg-NH<sub>2</sub>;  
 (N-Me)-Phe-Val-D-Phe-Ile-Phe-Thr-Tyr-Gly-Glu-Leu-Ala-D-Arg-NH<sub>2</sub>;  
 (Me<sub>2</sub>N)-Phe-Val-D-Phe-Ile-Phe-Thr-Tyr-Gly-Glu-Leu-Ala-D-Arg-NH<sub>2</sub>;  
 (N-Me)-Phe-Val-Phe-Ile-Phe-Thr-Tyr-Gly-Glu-Leu-Ala-D-Arg-NH<sub>2</sub>;  
 (Me<sub>2</sub>N)-Phe-Val-Phe-Ile-Phe-Thr-Tyr-Gly-Glu-Leu-Ala-D-Arg-NH<sub>2</sub>; and  
 (Me<sub>2</sub>N)-Phe-Val-Phe-Ile-Phe-Thr-Tyr-Gly-Glu-Leu-Ala-D-Arg-NH<sub>2</sub>;

and their pharmaceutically acceptable addition salts. In a most preferred embodiment, the compounds of the present invention are selected from the group consisting of

N-Phe-Val-Phe-Ile-Phe-Thr-Tyr-Gly-Glu-Leu-Gln-Arg-Leu-Gln-Lys-Glu-Arg-Asn-Lys-Gly-Gln-OH;

15



(Me<sub>2</sub>N)-Phe-Val-Phe-Ile-Phe-Thr-Tyr-Gly-Glu-Leu-Ala-D-Arg-NH<sub>2</sub>;

and their pharmaceutically acceptable addition salts.

The compounds of the present invention can be prepared by various methods known in the art such as by solid phase peptide synthesis or by classical solution phase synthesis. In the solid phase method, the peptide chain is sequentially constructed using a resin support, typically a polystyrene based, polyhipe based, or a polyacrylamide/Kieselguhr composite resin. The growing peptide chain is tethered to the resin support by a suitable, acid-labile molecular linker, such as hydroxymethylphenylacetamidomethyl (PAM), 4-methylbenzhydrylamino (MBHA), or hydroxymethylphenoxyacetoxy (HMPA) moieties. The peptide chain can then be cleaved from the linker, and thus the resin support, through acidolysis employing hydrogen fluoride, trifluoroacetic acid (TFA), trifluoromethanesulfonic acid (TFMSA), and the like.

Whether the gastrointestinal motor inhibitory polypeptides of this invention are prepared by solid phase or solution phase methods, the basic synthetic approach involves coupling of amino acid subunits through reaction of the carboxyl moiety of one suitably protected amino acid or peptide fragment with the amino group of another suitably protected amino acid or peptide fragment to form a new amide bond. In order to effect the coupling reaction, the carboxyl moiety must be activated. Activation is accomplished through the use of standard coupling reagents such as DCC, DIC, EDCC, BOP, HBTU, or PyBrOP. Except in the case of PyBrOP, an equimolar amount of HOBt may be added to suppress racemization of the activated amino acid component. Bases such as NMM, DIEA, or TEA may be used in those cases where it is necessary to employ the carboxylate salt of the corresponding amino acid for activation.

Alternatively, the peptides of this invention can be synthesized by coupling the active esters of the component amino acids. Such active esters include, for example, a pentachlorophenyl ester, a pentafluorophenyl ester, a *p*-nitrophenyl ester, and the like.

During the preparation of the peptides of this invention, other reactive functionalities of the amino acid components must be blocked with appropriate protecting groups. In general, the identity of the  $\alpha$ -amino protecting group dictates what type of side-chain protecting groups must be employed. For example, in the case where the  $\alpha$ -amino group is protected as its Boc derivative, side-chain protection is usually accomplished with ester, ether, or urethane derivatives of benzyl alcohol. Ester and ether derivatives of cyclohexanol have also been used with some success. In contrast, when the  $\alpha$ -amino group is protected as its Fmoc derivative, side chain functionality is generally protected as ester, ether, or urethane derivatives of *t*-butanol. Of course, alternative combinations of protecting groups may be employed especially when the peptides of this invention are synthesized by solution phase methodology.

Removal of the Fmoc  $\alpha$ -amino protecting group may be readily accomplished with a base, typically piperidine. The side chain protecting groups can be removed by treatment with TFA in the presence of an appropriate carbonium ion scavenger, which also cleaves the bond between the C-terminus of the peptide and the resin linker. The Boc protecting group is generally removed by treatment with dilute TFA. Following TFA cleavage, however, the  $\alpha$ -amino group is present as its TFA salt. In order to make the  $\alpha$ -amino group of the growing peptide chain reactive toward the next amino acid derivative, the resin-bound peptide is neutralized with a base such as TEA or DIEA. Strong acid, such as hydrofluoric acid or TFMSA, containing suitable scavengers is then used to deprotect the amino acid side-chains and to cleave the peptide from the resin support.

The compounds of the present invention while effective in the form of the free base may be formulated and administered in the form of pharmaceutically acceptable acid addition salts for purposes of stability, convenience of crystallization, increased solubility and the like. These acid addition salts are formed by conventional methods from suitable inorganic or organic acids such as hydrochloric, sulfuric, sulfonic, tartaric, fumaric, hydrobromic, glycolic, citric, maleic, phosphoric, succinic, acetic, nitric, benzoic, ascorbic, *p*-toluenesulfonic, benzenesulfonic, naphthalenesulfonic, propionic acid, and the like. Preferably, the acid addition salts are those prepared from hydrochloric acid, acetic acid, or succinic acid.

The compounds of the present invention can be combined with a pharmaceutically acceptable carrier to provide a pharmaceutical composition. Suitable carriers for the subject compounds as the free base include propylene glycol-alcohol-water, isotonic water, sterile water for injection (USP), emulphor™-alcohol-water, cremophor-EL™ or other suitable carriers known to those skilled in the art.

Suitable carriers for the acid addition salts of the subject compounds include isotonic water, sterile water for injection (USP), alone or in combination with other solubilizing agents such as ethanol, propylene glycol, or other conventional solubilizing agents known to those skilled in the art. A preferred carrier is an isotonic aqueous solution of the inventive compound.

The compounds of the present invention can be administered to mammals, e.g., animals or humans, in amounts effective to provide the desired gastrointestinal motor inhibitory activity. Since the activity of the compounds and the degree of the desired therapeutic effect vary, the dosage level of the compound employed

will also vary. The actual dosage administered will also be determined by such generally recognized factors as the body weight of the patient and the individual hypersensitiveness of the particular patient. Thus, the unit dosage for a particular patient (man) can vary from as low as about 0.1 µg per kg of body weight, which the practitioner may titrate to the desired effect. A preferred minimum dose for titration is 1 µg/kg body weight.

5 The compounds of the present invention can be administered by recognized parenteral routes, in the form of sterile solutions or suspensions, in the carriers previously described. These preparations should contain at least about 0.1%, by weight, of the inventive compound but this amount may be varied to between about 0.1% and about 50%, by weight, of the inventive compound. The compounds of the present invention are preferably administered intravenously and the dosage used will generally be in the range from about 0.1 µg to about 500  
10 mg, and preferably from about 1 µg to about 50 mg, per 70kg body weight. This dosage may be administered from 1 to 4 times daily.

The sterile solutions or suspensions may also include the following adjuvants: a sterile diluent, such as water for injection, saline solution, fixed oils, polyethylene glycol, glycerine, propylene glycol, or other synthetic solvent; antibacterial agents, such as benzyl alcohol or methyl paraben; antioxidants, such as ascorbic acid  
15 or sodium metabisulfite; chelating agents, such as ethylenediaminetetraacetic acid (EDTA); buffers, such as acetates, citrates or phosphates; and agents for the adjustment of tonicity, such as sodium chloride or dextrose. The parenteral preparations may be enclosed in ampules, disposable syringes, or multiple dosage vials made of glass or plastic.

Throughout this application, various publications have been referenced. The disclosures in these public-  
20 ations are incorporated herein by reference in order to more fully describe the state of the art.

The present invention is further illustrated by the following examples which are presented for purposes of demonstrating, but not limiting, the preparation of the compounds and compositions of this invention.

#### Example 1

25 [3-Phenylalanine, 13-leucine]motilin (Porcine), Pentakis-trifluoroacetate Salt

H-Phe-Val-Phe-Ile-Phe-Thr-Tyr-Gly-Glu-Leu-Gln-Arg-Leu-Gln-Glu-Lys-Glu-Arg-Asn-Lys-Gly-Gln-OH

30

The peptide was synthesized on 2.0 g. of Fmoc-L-Gln(Mbh)PepSyn KA resin (0.08 mequiv/g) by solid phase continuous flow techniques employing a MilliGen Model 9050 peptide synthesizer. All residues were coupled as Pfp esters of the Fmoc amino acids in the presence of HOBt, except for Thr which was the ODhbt ester.  
35 The side chain protection was as follows: Arg(Mtr), Glu(OtBu), Lys(Boc), Tyr(tBu), and Thr(tBu). Asn and Gln were left unprotected. A four-fold molar excess of the Fmoc amino acid OPfp/HOBt in DMF was used for coupling. Coupling efficiency was monitored by the Kaiser test. Coupling times ranged from 1-4 hours. After each coupling cycle, removal of the Fmoc-α-amino protecting group was accomplished with 20% piperidine in DMF. Following synthesis, the resin-bound peptide was washed with DCM and dried under vacuum overnight. De-  
40 blocking and cleavage of the peptide from the resin was performed at room temperature by shaking with anhydrous TFA containing 5% thioanisole, 3% ethanedithiol, and 2% anisole (20 ml. total) for 8 hours. The cleavage solution then was added dropwise to 250 ml. cold ether and the precipitated peptide collected by filtration to obtain 370 mg (70%) of the title peptide as a white powder. Peptide purification was achieved in three runs (typical load = 125 mg per run) by HPLC on a Waters Delta-Prep 3000 (Waters Associates) using two C-18  
45 columns in series (250 x 20mm, 15µ, Vydac). The solvent system was 0.1% TFA with a 30 minute gradient to 60% acetonitrile/40% TFA(0.1 %) at 20 ml/min with UV detection at 220 nm. The purity of individual fractions was assessed by analytical HPLC (30 minute gradient, 100% TFA(0.1%) to 100% acetonitrile, 1 ml/min, 214 nm; R<sub>t</sub> = 16.22 min) and capillary zone electrophoresis. Pure fractions (>95%) were pooled and lyophilized to provide 145 mg (27%) of the title peptide as a flocculent white powder.

50 AAA: Asx 1.01 (1), Thr 0.84 (1), Glx 6.01 (6), Gly 2.05 (2), Val 0.97 (1), Ile 0.92 (1), Leu 2.02 (2), Tyr 0.99 (1), Phe 2.95 (3), Lys 2.13 (2), Arg 2.00 (2). FAB-MS: (M+H)<sup>+</sup> calcd 2732, found 2732.

55

## Exempl 2

[3-Phenylalanine]motilin-(1-12)-peptide Amide (Porcine), Bis-trifluoroacetate Salt.

5

H-Phe-Val-Phe-Ile-Phe-Thr-Tyr-Gly-Glu-Leu-Gln-Arg-NH<sub>2</sub>

The peptide was synthesized on 1.0 g. of MBHA resin (0.27 mequiv/g) using a MilliGen Model 9600 peptide synthesizer. All Boc amino acids were coupled following preactivation with an equimolar amount of DIC in DMF / DCM. Boc-L-Gln-OH was preactivated in the presence of 1.5 equivalents of HOBt to suppress dehydration of the amide side chain. The side chain protection was as follows: Arg(Tos), Glu(OBzl), Tyr(2-Br-Cbz), and Thr(Bzl). A 6.67-fold molar excess of the Boc amino acid was used for coupling. Coupling strategy was determined by the Analysis Expert System in the Milligen Biodrive v 1.05 software package. Protocols were as follows: Arg<sup>12</sup> (2 hr, double couple); Gln<sup>11</sup> (2 hr, single couple); Leu<sup>10</sup> (2 hr, single couple); Glu<sup>9</sup> (2 hr, single couple); Gly<sup>8</sup> (2 hr, single couple); Tyr<sup>7</sup> (2 hr, single couple); Thr<sup>6</sup> (2 hr, single couple); Phe<sup>5</sup> (2 hr, double couple); Ile<sup>4</sup> (2 hr, double couple); Phe<sup>3</sup> (2 hr, double couple); Val<sup>2</sup> (2 hr, double couple); Phe<sup>1</sup> (2 hr, double couple). Coupling efficiency was monitored by the Kaiser test. After each cycle, removal of the Boc- $\alpha$ -amino protecting group was accomplished with TFA/anisole/DCM (45:2.5:52.5). The peptide was converted to its free base by washing with 10% DIEA in DCM. Following synthesis, the resin-bound peptide was dried under vacuum overnight. Deblocking and cleavage of the peptide from the resin was performed at -5°C for 2 hours by stirring the resin with anhydrous HF containing 8.3% dimethylsulfide and 8.3% anisole (10 ml. total). Following evaporation of the cleavage solution, the residue was partitioned between ether (150 ml) and water (150 ml). The aqueous layer was washed several times with ether (4 x 150 ml) and lyophilized to provide the title peptide as a white powder. Peptide purification was achieved in two runs (typical load = 115 mg per run) by HPLC on a Waters Delta-Prep 3000 (Waters Associates) using two C-18 columns in series (250 x 20mm, 15 $\mu$ , Vydac). The solvent system was 0.1% TFA with a 30 minute gradient to 60% acetonitrile/40% TFA(0.1%) at 20 ml/min with UV detection at 220 nm. The purity of individual fractions was assessed by analytical HPLC (30 minute gradient, 100% TFA(0.1%) to 100% acetonitrile, 1 ml/min, 214 nm; R<sub>t</sub>=17.05 min) and capillary zone electrophoresis. Pure fractions (>95%) were pooled and lyophilized to provide 97 mg (21%) of the title peptide as a flocculent white powder.

AAA: Thr 0.95 (1), Glx 2.05 (2), Gly 1.02 (1), Val 0.85 (1), Ile 0.95 (1), Leu 1.06 (1), Tyr 1.03 (1), Phe 3.01 (3), Arg 1.06 (1). FAB-MS: (M+H)<sup>+</sup> calcd 1519, found 1519.

## 35 Example 3

[1-N-Methylphenylalanine, 3-phenylalanine, 13-leucine] motilin-(1-14)-peptide (Porcine), Bis-trifluoroacetate Salt.

40

(N-Me)-Phe-Val-Phe-Ile-Phe-Thr-Tyr-Gly-Glu-Leu-Gln-Arg-Leu-Gln-OH.

The peptide was synthesized on 0.9 g. of Fmoc-L-Gln(Trt)PAC resin (0.28 mequiv/g) by solid phase continuous flow techniques employing a MilliGen Model 9050 peptide synthesizer. The resin was mixed with 5.4 g of glass beads (acid washed, 150-212 microns), dry-packed into a continuous flow column, and swelled with DMF for 1 hr prior to use. Fmoc-MePhe-OH was coupled by preactivation with BOP and HOBt (1:1:1) in the presence of 0.6M NMM in DMF. Fmoc-L-Thr-OH was coupled as its ODhbt ester in the presence of HOBt. All other residues were coupled as Pfp esters of the Fmoc amino acids in the presence of HOBt. The side chain protection was as follows: Arg(Mtr), Glu(OtBu), Tyr(tBu), and Thr(tBu). Gln was left unprotected. A four-fold molar excess of the Fmoc amino acid derivative in DMF was used for coupling. Coupling efficiency was monitored by the Kaiser test. Typical coupling times ranged from 1-4 hours. After each cycle, removal of the Fmoc- $\alpha$ -amino protecting group was accomplished with 20% piperidine in DMF. Following synthesis, the resin-bound peptide was washed with DCM and dried under vacuum overnight. Deblocking and cleavage of the peptide from the resin was performed at room temperature by shaking with anhydrous TFA containing 5% thioanisole, 3% ethanedithiol, and 2% anisole (20 ml. total) for 8 hours. The cleavage solution then was added dropwise to 250 ml. cold ether and the precipitated peptide collected by filtration to obtain the title peptide as a white powder. Peptide purification was achieved in three runs (typical load = 100 mg per run) by HPLC on a Waters

Delta-Prep 3000 (Waters Associates) using two C-18 columns in series (250 x 20mm, 15µ, Vydac). The solvent system was 0.1% TFA with a 30 minute gradient to 60% acetonitrile/40% TFA(0.1%) at 20 ml/min with UV detection at 220 nm. The purity of individual fractions was assessed by analytical HPLC (30 minute gradient, 100% TFA(0.1%) to 100% acetonitrile, 1 ml/min, 214 nm;  $R_t$ =17.99 min) and capillary zone electrophoresis.

5 Pure fractions (>95%) were pooled and lyophilized to provide 86 mg (18%) of the title peptide as a flocculent white powder.

AAA: Thr 0.87 (1), Glx 3.13 (3), Gly 1.13 (1), Val 0.75 (1), Ile 0.96 (1), Leu 2.10 (2), Tyr 0.99 (1), Phe 1.97 (2), Arg 1.03 (1). FAB-MS: (M+H)<sup>+</sup> calcd 1775, found 1775.

#### 10 Example 4

##### Determination of motilin receptor binding affinity

The motilin receptor binding affinity of the peptides of this invention was determined by using the general procedure of Bormans, Peeters and Vantrappen, Regul. Pept., 15, 143-153 (1986). The ability of the peptides to displace [<sup>125</sup>I-Tyr<sup>7</sup>,Nle<sup>13</sup>]motilin(porcine) bound to rabbit antral smooth muscle membranes, was determined by testing twice, each time in duplicate, at concentrations ranging from 10<sup>-11</sup> to 10<sup>-4</sup> M. The concentration displacing 50% of the label (IC<sub>50</sub>) was determined by fitting the data to the equation describing displacement, assuming a single class of motilin receptors to which labeled and non-labeled motilin bind with equal affinity and non-cooperatively. Fitting was performed using the iterative least-squares procedure of the SAS-software package (SAS Institute, Inc., Cary, NC, USA). From a large series of control experiments the dissociation constant of motilin itself was calculated as 0.75 nM (pK<sub>d</sub> = 9.12), and this value was used for all calculations. The concentration displacing 50% of the label is expressed using its negative logarithm (pIC<sub>50</sub>).

20

#### 25 Example 5

##### Rabbit duodenal smooth muscle strip tissue bath assay

The contractile response of segments of rabbit duodenum was determined isotonicly in the tissue bath according to the procedure of Depoortere et al., J. Gastrointestinal Motility, 1, 150-159 (1989). The experimental protocol consisted of an equilibration period of 1 hour; a challenge with 10<sup>-4</sup> M acetylcholine followed by a wash-out period; a cumulative dose-response curve of a compound with, at the end, the addition of 10<sup>-7</sup> M motilin; and finally 10<sup>-4</sup> M acetylcholine. If the final response to 10<sup>-4</sup> M acetylcholine differed by more than 5% from the initial response, the results were discarded. The compounds were tested in the concentration range 10<sup>-11</sup> to 10<sup>-4</sup> M. The point corresponding to 50% of the maximal response to motilin (E<sub>max</sub>) was determined by fitting the equation  $E = E_{max} (1 + EC_{50}/[L])$  through the data points. For weakly active compounds 90% of the response to 10<sup>-7</sup> M motilin was used as E<sub>max</sub>. The dose giving 50% of the response is expressed using its negative logarithm (pEC<sub>50</sub>).

30

35

#### 40 Example 6

##### Motilin Receptor Antagonism

To determine motilin receptor antagonism, the contractile response of segments of rabbit duodenum to motilin was determined isotonicly in the tissue bath in the presence of a fixed concentration of the compound of interest. The experimental protocol consisted of an equilibration period of 1 hour; a challenge with 10<sup>-4</sup> M acetylcholine followed by a wash-out period; a cumulative motilin dose-response curve in the presence of the motilin receptor antagonist; and finally a challenge with 10<sup>-4</sup> M acetylcholine. If the final response to 10<sup>-4</sup> M acetylcholine differed by more than 5% from the initial response, the results were discarded. The point corresponding to 50% of the maximal response to motilin (E<sub>max</sub>) was determined by fitting the equation

50

$$E = E_{max} (1 + EC_{50}/[L])$$

through the data points. The dose of motilin giving 50% of the response is expressed using its negative logarithm (pEC<sub>50</sub>). Compounds of interest were tested at concentrations of 10<sup>-8</sup> to 10<sup>-5</sup> M.

For example, in the presence of 10<sup>-8</sup> M [Phe<sup>3</sup>, Leu<sup>13</sup>]pMOT(1-14) the dose-response curve of motilin was shifted by about one log unit. Thus the pEC<sub>50</sub> was 7.26 ± 0.21 as compared to the control value of 8.33 ± 0.17. [Phe<sup>3</sup>, Leu<sup>13</sup>]pMOT(1-14) at 10<sup>-5</sup> M completely blocked the full contractile response to motilin. The competitive nature of the interaction was confirmed by Schild-analysis (slope: 0.86 ± 0.06).

55

## Motilin Receptor Antagonists in Binding and in Contractility Experiments

Compound	pEC50	pIC50
[Phe <sup>3</sup> , Leu <sup>13</sup> ]pMOT	<4.5	9.11
[Ile <sup>3</sup> , Leu <sup>13</sup> ]pMOT	<4.5	7.82
[Phe <sup>3</sup> , Leu <sup>13</sup> ]pMOT(1-14)	<4.5	7.79
[Leu <sup>3</sup> , Leu <sup>13</sup> ]pMOT(1-14)	<4.5	6.75
[p-I-Phe <sup>3</sup> , Leu <sup>13</sup> ]pMOT(1-14)	<4.5	7.36
[Thi <sup>3</sup> , Leu <sup>13</sup> ]pMOT(1-14)	<4.5	7.59
[Cha <sup>3</sup> , Leu <sup>13</sup> ]pMOT(1-14)	<4.5	7.68
[2-Nal <sup>3</sup> , Leu <sup>13</sup> ]pMOT(1-14)	<4.5	7.56
[D-Phe <sup>3</sup> , Leu <sup>13</sup> ]pMOT(1-14)	<4.5	8.09
[Pal <sup>3</sup> , Leu <sup>13</sup> ]pMOT(1-14)	<4.5	6.80
[Phe <sup>3</sup> , D-Arg <sup>12</sup> , Leu <sup>13</sup> ]pMOT(1-14)	<4.5	7.09
[Phe <sup>3</sup> , Leu <sup>4</sup> , Leu <sup>13</sup> ]pMOT(1-14)	<4.5	8.40
[Phe <sup>3</sup> , Ala <sup>5</sup> , Leu <sup>13</sup> ]pMOT(1-14)	<4.5	7.80
[Phe <sup>3</sup> , Phe <sup>7</sup> , Leu <sup>13</sup> ]pMOT(1-14)	<4.5	7.51
[Phe <sup>3</sup> , D-Ala <sup>8</sup> , Leu <sup>13</sup> ]pMOT(1-14)	<4.5	7.31
[Phe <sup>3</sup> , Ala <sup>11</sup> , Leu <sup>13</sup> ]pMOT(1-14)	<4.5	7.80
[Leu <sup>2</sup> , Phe <sup>3</sup> , Leu <sup>13</sup> ]pMOT(1-14)	<4.5	7.47
[Phe <sup>3</sup> , Leu <sup>13</sup> , Lys <sup>14</sup> ]pMOT(1-14) amide	<4.5	8.80
[D-Phe <sup>1</sup> , Phe <sup>3</sup> , Leu <sup>13</sup> ]pMOT(1-14)	<4.5	6.64
[Cha <sup>1</sup> , Phe <sup>3</sup> , Leu <sup>13</sup> ]pMOT(1-14)	<4.5	7.53

# **Motilin Receptor Antagonists in Binding and in Contractility Experiments** (continued)

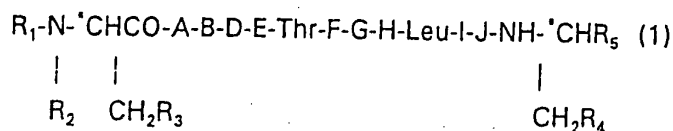
Compound	pEC50	pIC50
[Phe <sup>3</sup> ]pMOT(1-12) amide	<4.5	7.56
[N-MePhe <sup>1</sup> , Phe <sup>3</sup> , Leu <sup>3</sup> ]pMOT(1-14)	<4.5	7.97
[Phe <sup>3</sup> , Cha <sup>5</sup> , Leu <sup>13</sup> ]pMOT(1-14)	<4.5	7.60
[Phe <sup>3</sup> , Leu <sup>13</sup> , D-Gln <sup>14</sup> ]pMOT(1-14) amide	<4.5	9.01

\* pMOT = porcine motilin

While we have represented a number of embodiments of this invention, it is apparent that the basic construction can be altered to provide other embodiments which utilize the invention without departing from the spirit and scope of the invention. All such modifications and variations are intended to be included within the scope of the invention as defined in the appended claims rather than the specific embodiments which have been presented by way of example.

## **Claims**

1. Polypeptides having gastrointestinal motor inhibitory activity represented by the formula:



including optically active isomeric forms and the pharmaceutically acceptable acid addition salts thereof wherein:

A is the L-stereoisomer of a lipophilic aliphatic or alicyclic amino acid;

B is selected from the group consisting of L and D aromatic, heteroaromatic, lipophilic aliphatic, and alicyclic amino acids;

D is the L-stereoisomer of a lipophilic aliphatic or alicyclic amino acid;

E is the L-stereoisomer of an aromatic, aliphatic, or alicyclic amino acid;

F is the L-stereoisomer of an aromatic or heteroaromatic amino acid;

G is glycine or D-alanine;

H is L-glutamic acid or L-glutamine;

I is L-glutamine, L-glutamic acid, or L-alanine;

J is a direct bond between I and group -NH- or is selected from the group consisting of Z, Z-Leu, Z-Leu-Gln, Z-Leu-Gln-Glu, Z-Leu-Gln-Glu-Lys, Z-Leu-Gln-Glu-Lys-Glu, Z-Leu-Gln-Glu-Lys-Glu-Arg, Z-Leu-Gln-Glu-Lys-Glu-Arg-Asn, Z-Leu-Gln-Glu-Lys-Glu-Arg-Asn-Lys, and Z-Leu-Gln-Glu-Lys-Glu-Arg-Asn-Lys-Gly, wherein Z is selected from the group consisting of arginine, D-arginine, D-homoarginine, D-lysine, D-ornithine, D-2,4-diaminobutyric acid, D-glutamine, D-asparagine, and D-alanine;

R<sub>1</sub> and R<sub>2</sub> are independently hydrogen or lower-alkyl;

R<sub>3</sub> is selected from the group consisting of lower-alkyl, cycloalkyl, substituted and unsubstituted aryl, and heteroaryl, wherein the aryl group may be substituted with one or more substituents selected from the group consisting of halogen, hydroxy, and lower-alkoxy;

$R_4$  is selected from the group consisting of  $-\text{CH}_2\text{CONH}_2$ , aminoalkyl groups containing from 1 to 3 carbon atoms, and guanidinoalkyl groups containing 2 or 3 carbon atoms;

$R_5$  is  $-\text{COOH}$  or  $-\text{CONH}_2$ ; and

the symbol \* represents an asymmetric carbon atom which may be in the D or L configuration, and each lower-alkyl group contains from 1 to 4 carbon atoms, with the proviso that  $R_4$  is  $-\text{CH}_2\text{CONH}_2$  only when J is Z-Leu or Z-Leu-Gln-Glu-Lys-Glu-Arg-Asn-Lys-Gly.

2. The polypeptide according to claim 1, wherein  $(R_1)(R_2)\text{N}^*\text{CH}(\text{CH}_2\text{R}_3)\text{CO}-$  is selected from the group consisting of L-phenylalanine, D-phenylalanine, L-cyclohexylalanine, and D-cyclohexylalanine.
3. The polypeptide according to claim 1, wherein the amino acid of A is selected from the group consisting of valine, isoleucine, leucine, norvaline, norleucine, and cyclohexylalanine.
4. The polypeptide according to claim 1, wherein the amino acid of B is selected from the group consisting of phenylalanine, p-fluorophenylalanine, p-chlorophenylalanine, p-bromophenylalanine, p-iodophenylalanine, tyrosine, p-methoxyphenylalanine, 1-naphthylalanine, 2-naphthylalanine, tryptophan,  $\beta$ -2-thienylalanine,  $\beta$ -3-pyridylalanine,  $\alpha$ -aminobutyric acid, norvaline, norleucine, leucine, and cyclohexylalanine.
5. The polypeptide according to claim 1, wherein the amino acid of D is selected from the group consisting of isoleucine, valine, leucine, norvaline, norleucine, and cyclohexylalanine.
6. The polypeptide according to claim 1, wherein the amino acid of E is selected from the group consisting of phenylalanine, p-fluorophenylalanine, p-chlorophenylalanine, p-bromophenylalanine, p-iodophenylalanine, tyrosine, p-methoxyphenylalanine, 1-naphthylalanine, 2-naphthylalanine, leucine, alanine, and cyclohexylalanine.
7. The polypeptide according to claim 1, wherein the amino acid of F is selected from the group consisting of tyrosine, phenylalanine, p-methoxyphenylalanine, histidine, tryptophan,  $\beta$ -2-thienylalanine, and  $\beta$ -3-pyridylalanine.
8. The polypeptide according to claim 1, wherein J is a direct bond between I and group  $-\text{NH}-$ , or is selected from the group consisting of Z-Leu, Z-Leu-Gln-Glu, Z-Leu-Gln-Glu-Lys-Glu, Z-Leu-Gln-Glu-Lys-Glu-Arg-Asn, and Z-Leu-Gln-Glu-Lys-Glu-Arg-Asn-Lys-Gly and Z is selected from the group consisting of arginine, D-arginine, and D-glutamine.
9. The polypeptide according to claim 1, wherein  $R_3$  is selected from the group consisting of methyl, ethyl, n-propyl, iso-propyl, n-butyl, cyclohexyl, phenyl, p-fluorophenyl, p-chlorophenyl, p-bromophenyl, p-iodophenyl, p-hydroxyphenyl, p-methoxyphenyl, 1-naphthyl, 2-naphthyl, 3-indolyl, 2-thienyl, and 3-pyridyl.
10. The polypeptide according to claim 1, wherein  $R_4$  is selected from the group consisting of  $-\text{CH}_2\text{CONH}_2$ , and aminoalkyl groups containing from 1 to 3 carbon atoms.
11. Polypeptides according to any one of the preceding claims for use in therapy.
12. A process for the preparation of polypeptides having a composition according to claim 1, comprising reacting with a strong acid a polypeptide of formula (1) which is linked to a suitable resin support and which contains protecting groups on amino acids having reactive functionalities so as simultaneously to cleave the polypeptide from said resin support and remove said protecting groups.



European Patent  
Office

## EUROPEAN SEARCH REPORT

Application Number

DOCUMENTS CONSIDERED TO BE RELEVANT			EP 94305706.7
Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (Int. Cl. 6)
A	EP - A - 0 378 078 (SANWA KAGAKU KENKYUSHO CO) * Claims 1-8 *	1-12	C 07 K 14/63 A 61 K 38/10
A	EP - A - 0 355 720 (SANWA KAGAKU KENKYUSHO CO) * Claims 1-3 *	1-12	
A	EP - A - 0 507 573 (SANWA KAGAKU KENKYUSHO CO) * Claims 1,7 *	1-12	
A	CHEMICAL ABSTRACTS, vol. 112, no. 11, 1990, March 12, Columbus, Ohio, USA SANWA KAGAKU KENKYUSHO CO "Recombinant manufacture of motilin-like polypeptide" page 240, no. 93 249g; & JP-A-01 102 096	1-12	
A	CHEMICAL ABSTRACTS, vol. 115, no. 11, 1991, September 15, Columbus, Ohio, USA SANWA KAGAKU KENKYUSHO CO "Motilin-like polypeptides for treatment of digestive tract disorder" page 76, no. 106 013q; & JP-A-02 311 495	1-12	TECHNICAL FIELDS SEARCHED (Int. Cl. 6)  C 07 K 14/00 A 61 K 38/00
The present search report has been drawn up for all claims			
Place of search VIENNA		Date of completion of the search 08-11-1994	Examiner BRUS
<p>CATEGORY OF CITED DOCUMENTS</p> <p>X: particularly relevant if taken alone Y: particularly relevant if combined with another document of the same category A: technological background O: non-written disclosure P: intermediate document</p> <p>T: theory or principle underlying the invention E: earlier patent document, but published on, or after the filing date D: document cited in the application L: document cited for other reasons &amp;: member of the same patent family, corresponding document</p>			

EPO FORM 1503 01.92 (P0401)